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819305

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/819,305	01/09/92	ANDERSON	P 3117-081

EXAMINER: KIM, K

ART UNIT: 1813 | PAPER NUMBER: 9

18N1/0802

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DATE MAILED: 08/02/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on Statement 6/1/93 Amend & IDS 4/14/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 90, 91 and 93-97 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 1-89 and 92 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 90, 91 and 93-97 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Applicant's amendments and arguments filed April 14, 1993 have been carefully considered and all of the rejections over claims 1 and 92 are rendered moot in view of the cancellation of the claims.

Further, the objection to the specification under 35 USC 112, first paragraph, set forth on page 2 of the Office action mailed October 15, 1992 has been overcome in view of the presence of S. pneumoniae 6A on page 51, Table 15 of the specification as was pointed out by Applicant on page 2 of the amendment filed April 14, 1993.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1) However, claims 90 and 96 remain rejected under 35 USC 102(e) over Jennings et al 4,356,170; claims 91 and 93-95 remain rejected under 35 USC 103 over Jennings et al and claim 97 remain rejected under 35 USC 103 over Jennings et al in view of Uchida et al (1972) as set forth on pages 2-4 of the Office action mailed October 15, 1992.

Applicant urges that

> "the presently claimed invention is in no way anticipated by Jennings and, in fact, is clearly contrary to the teachings of Jennings. Examiner's attention is directed to the presently pending claims 90-91 and 93-97. As clearly recited in all the pending claims, the present invention is an cross-linked immunogenic conjugate which is the reductive amination product of a capsular polymer of Streptococcus pneumoniae having at least two carbonyl groups directly covalently linked, through the carbonyl groups to a bacterial toxin or toxoid.
>
> Examiner's attention is directed further to the teaching of the present specification at page 8, line 25 through page 9, line 2; see also Example 11 at pages 50-51. As explained therein, because the capsular polymer employed in the presently claimed conjugated have at least 2 carbonyl groups, conjugation of such polymers according to the method of the present invention results in cross-linked compositions. The cross-linked conjugate compositions are prepared by covalently attaching the reducing end groups of a capsular polymer obtained from

S. pneumoniae, to amine groups of a bacterial toxin or toxoid.

In complete contrast to the presently claim crossed-linked conjugates, the Jennings references describes antigenic conjugates in which a capsular polymer is attached via a terminally introduced aldehyde group to an amine group of tetanus toxoid. The method of attachment is asserted to be specific in that the only covalent attachment between the toxoid and the capsular polysaccharide occurs at the single terminally located aldehyde group of the polysaccharide (Jennings, at col. 3, lines 55-63; see also, id. at col.2, lines 34-38. The reference further asserts that the method of coupling employed "avoids cross-linking" between the polysaccharide and the protein. Jennings at col.2, lines 38-39; see also, id. at col.3 lines 62-63. In addition, as clearly recited in the claims of the Jennings patent, the conjugates prepared as taught therein as "non-cross-linked" conjugates. E.g., independent claims 1 and 11.

Applicants emphatically point out that the Examiner's assertion that the conjugates of Jennings "would inherently possess at least two carbonyl groups" is completely erroneous. The Jennings reference teaches conjugation via a single aldehyde group on the end of the polysaccharide. The clear focus of Jennings is to generate a single aldehyde group. This is accomplished by Jennings by pretreatment of the capsular polymer or polysaccharide which otherwise would yield more than one aldehyde, so that upon treatment with periodate, only one aldehyde is obtained. See, Jennings at col. 3, lines 10-17,22-27, and at col. 4, lines 49-59 (pretreatment of the meningococcal group A polysaccharide).

In addition, Jennings also teaches mild oxidation of the polysaccharide in order to selectively form only a single terminal aldehyde group. Jennings at col. 3, lines 28-39. See Jennings, at col. 5, lines 38-54 which specifically teaches mild periodate conditions so as to produce only a single aldehyde on the polysaccharides of meningococcal C group. See also, col. 6, lines 5-9.

Thus, there is no affirmative teaching in Jennings concerning cross-linking. Rather, the only teaching in Jennings about cross-linking is a very negative view which clearly teaches away from cross-linking." See pages 3-4 of the amendment filed April 14, 1993.

However, Applicant's particular attention is drawn to the fact that the instant claimed limitation for "at least two carbonyl groups" are inherent in the teachings of Jennings et al for the oxidation of carbohydrates wherein the vicinal hydroxy groups of a saccharide moiety are oxidized to generate two carbonyl groups. See column 2, line 44 of Jennings et al. As such, applicant's arguments are not deemed persuasive.

Further, Applicant urges that

> "Applicants do not agree and respectfully submit that this rejection is plainly in error as a matter of fact and law. As explained more fully above in Section II A, in complete contrast to the presently claimed cross-linked conjugates, the conjugates disclosed by Jennings are non-cross-linked. In fact, as further detailed above, Jennings teaches that a single terminal aldehyde group is introduced into a capsular polymer by means of controlled mild oxidation and is attached to an amine of tetanus toxin in a process designed particularly to avoid cross-linking of the products formed. Thus, it is clear that instead of suggesting the presently claimed cross-linked conjugates, Jennings, in fact, teaches away from the presently claimed subject matter.
>
> As the Court of Appeals for the Federal Circuit has made emphatically clear, where a reference teaches away from the claimed invention, such reference in no way evidences the obviousness of such invention. E.g.; Raytheon Co. v. Roper Corp., 724 F.2d 957, 961 (Fed. Cir. 1983), cert. denied,469 U.S. 835 (1984); accord, Dow Chemical Co. vs. U.S., 18 U.S.P.Q.2d 1657, 1662 (Ct. Cl. 1990); In re Hedges, 783 F.2d 1038, 1041 (Fed. Cir. 1986)." See pages 5-6 of the amendment filed April 14, 1993.

Examiner agrees with the Applicant's summary of Jennings et al to the extend of the use of mild oxidation condition. Nevertheless, Jennings et al teach cross-linked polysaccharide to immunogenic conjugate as vaccines and as such, Examiner disagrees with Applicant's contention that such teaches away from the claimed cross-linked polysaccharide-immunogenic carrier conjugates especially in view of the references teachings for the polysaccharide having at least two carbonyl groups recited in the claims.

Further, Applicant urges that

> "Uchida adds nothing to the Jennings reference to make such conjugates obvious. Uchida merely describes two non-toxic proteins produced by Corynebacterium diphtheriae. These non-toxic proteins, designated CRM 45 and CRM 197, cross-react with diphtheria anti-toxin. Thus, the Uchida reference merely shows that the toxoid employed in one embodiment of the present invention, i.e., CRM 197, exists. Nothing in this reference suggests that this toxoid should be coupled to capsular polymers, much less to a capsular polymer to form a cross-linked conjugates as presently claimed".

See pages 6-7 of the amendment filed April 14, 1993.

While the teachings of Uchida are drawn to CRM197 and not to the conjugates thereof as Applicant pointed out, such teachings were applied in combination and as a functional equivalent to the carrier of Jennings et al. Therefore, Applicant's arguments have been carefully and fully considered but are not deemed persuasive for the reasons set forth above.

2) Claims 90, 91 and 93-97 remain rejected under the judicially created doctrine of obviousness-type double patenting over the claims of 4,673,574; 4,761,283; 4,808,700; 4,902,506; and 5,097,020 and claims 90, 91 and 93-96 remain provisionally rejected over the claims to 07/205,132 as set forth on pages 4-5 of the Office action mailed October 15, 1992.

Applicant contends that

> "these rejections are clearly improper. Obviousness-type double patenting is a doctrine intended to prevent improper timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not "patentably distinct" from the claims of a first patent to the same inventor or owned by a common assignee. E.g., In re Braat, 937 F.2d 586,592 (Fed. Cir. 1991).
>
> As explained by the Court of Appeals for the Federal Circuit, when considering a double patenting rejection, the relevant inquiry is to compare the presently claimed subject matter with what was claimed in the first of the two patents and not what was disclosed in the specification of the first. In re Kaplan, 789 F.2d 1574, 1579 (Fed. Cir. 1986). Thus, the claims of the first patent must be compared with those of the application to determine whether they both are directed to the same invention or even a "mere variation of that invention which would have been obvious to those of ordinary skill in the relevant art." 784 F.2d at 1580. Further, the Kaplan Court stated emphatically, that "there must be clear evidence to establish why the variation would have been obvious which can properly qualify as 'prior art'." Id. (emphasis added).
>
> Based on a comparison of the relevant claims, it is clear that the subject matter of the claims of the present application is not an obvious variant of that of the cited claims of the cited Anderson I, Anderson II and Eby I, Anderson and Eby II combined with those of the Anderson and Clements patent. With respect, Applicants submit that the Examiner has overlooked and failed to appreciate the most critically important feature of the presently claimed invention. As detailed

above in Section IIA, the presently claimed invention, is a cross-linked immunogenic conjugate. The cross-linked immunogenic conjugates comprise reductive amination products of (1) the capsular polymer of a Streptococcus pneumoniae serotype having at least two carbonyl groups, covalently attached to (2) a bacterial toxin or toxoid. According to the present specification, at least two carbonyl groups, which provide for cross-linking of the capsular polymer with the protein moiety, are generated by treatment of the capsular polymer with an oxidizing agent. As explained further, the present conjugates having a lattice or network structure, provide "extremely high levels of anti-capsular polymer antibodies in infants." Abstract at lines 14-17. Additionally, the cross-linked conjugates comprise an intact capsular polymer or an S. pneumoniae serotype, rather than a capsular polymer fragment. The present claims are directed to compositions in which an intact capsular polymer is attached to a toxin or toxoid resulting in a cross-linked conjugate. None of the cited Anderson or Anderson/Clements patents suggest, much less teach, use of intact capsular polymers.

The claims of Anderson I, as well as Anderson II, which are directed to immunogenic conjugates in which a capsular polymer fragment is covalently attached, via a reductive amination process, to a bacterial toxin or toxoid do not suggest the present claims. The claims of Anderson I require specifically that the capsular polymer fragment have a chain length of 10-30 monomeric units and be derived from the capsular polymer of S.pneumoniae or H. influenzae. The claims of Anderson II require that the capsular polymer fragment be derived from H. influenza type b, E. coli, Neisseria meningitis and S. pneumoniae and that the toxin is CRM 197. The claims of Anderson and Eby I and Anderson and Eby II are directed to conjugates, which like the presently claimed conjugates are cross-linked conjugates. Unlike the presently claimed conjugates, however, the conjugates of Anderson and Eby I and II require a capsular polymer fragment. In particular, the claims of Anderson and Eby I, require that the capsular polymer fragment have a chain length of 10-30 monomeric units and be derived from the capsular polymer of S. pneumoniae or H. influenzae. The claims of Anderson and Eby II require that the capsular polymer fragment be obtained by a process entailing two steps, i.e., treating a capsular polymer with acid, base or enzyme to fragment the polymer and generating at least 2 carbonyl groups by treating with an oxidizing agent. Finally, the claims of Anderson and Clements require that capsular polymer fragment be attached to a novel non-toxic LT-BNT subunit of the heat labile enterotoxin of E. coli.

The present claims, in contrast, are directed to cross-linked immunogenic conjugates which comprise reductive amination products of (1) a intact capsular polymer of S. pneumoniae, having at least two carbonyl groups, obtained by treating said capsular polymer with an oxidizing agent, covalently attached to (2) a bacterial toxin or toxoid.

> Nothing in the claims of the cited patents, alone or in combination, would have suggested the presently claimed conjugates. Moreover, nothing in the claims of the cited combination of patents would have established why the claimed conjugates would have been obvious. This falls far short of the test for obviousness-type double patenting as enunciated by the Court of Appeals in In re Kaplan, which emphatically held that "there must be some clear evidence to establish why the variation would have been obvious which can properly qualify as 'prior art'." 789 F.2d at 1580.
>
> If, however, contrary to Applicants' reasoning above, the Examiner persists, Applicants would be amenable to submit a terminal disclaimer by the common assignee of the subject matter of this present application over Anderson I and II and Anderson and Eby I and II. More than such terminal disclaimer is certainly not necessary.
>
> With respect to the provisional rejection based on the Anderson and Clements Application, Applicants respectfully submit, that for reasons detailed above with respect to the claims of the Anderson and Clements patent, this rejection is in error and should be withdrawn." See pages 9-11 of the amendment filed April 14, 1993.

Applicant's attention is drawn to the fact that all of the related patents and application are drawn to cross-linked immunogenic conjugates wherein the polysaccharides are oxidized to provide at least two carbonyl groups. See above comments on vicinal hydroxy groups.

Further, the Applicant's contention of the chain length limitation set forth in "Anderson I" as distinct from the presently claimed capsular polymer is not understood. While the "Anderson I" does claim fragments of the polysaccharides, they are nevertheless polysaccharides which impart immunogenicity when conjugated to a carrier. As such are functionally equivalent species of the genus claimed in the instant application which anticipate the claimed invention. Even if "intact" was a claimed limitation to the instantly claimed invention, the claims are rendered at least clearly obvious for the same reasons set forth above. Further, the carriers of the recited patents and application are species of broadly recited bacterial toxin or toxoid of the instant application wherein the claims to Anderson and Clements' "novel non-toxic LT-BNT

subunit of the heat labile enterotoxin of E. coli" constitute such a species which anticipates the genus claimed or at least clearly render obvious instantly claimed invention as a whole.

Therefore, Applicant's arguments have been fully considered but are not deemed persuasive for the reasons set forth above.

3) Applicant's statement under 37 CFR 1.78(c) has been carefully considered and the following rejection is set forth.

4) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (f) he did not himself invent the subject matter sought to be patented.

a) Claims 90, 96 and 92 are rejected under 35 U.S.C. § 102(f) as being anticipated by Anderson et al 4,808,700.

The patent teaches the instant invention at columns 29-32, sections 6.5 and 6.6.

b) Claims 91 and 93-95 are rejected under 35 U.S.C. § 103 as being unpatentable over Anderson et al 4,808,700.

Further the patent exemplifies S. pneumoniae serotype 3,6,12 and 19 and therefore the substitution of various serotypes of S. pneumoniae in the conjugate taught are at least clearly obvious to one of ordinary skill in the art in view of functional equivalence taught by the reference with the reasonable expectation of eliciting desired immunity against the particular serotype of the S. pneumoniae specified in the conjugate.

5) The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax number is (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay K. Kim, Ph.D whose telephone number is (703) 308-3881.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Kim/sg
August 2, 1993

Kay K. Kim

KAY K. KIM
PRIMARY EXAMINER
GROUP 1800